

## TITLE OF THE INVENTION

## METHOD FOR THE PREVENTION AND/OR TREATMENT OF ATHEROSCLEROSIS

## FIELD OF THE INVENTION

5                   The instant invention involves the use of inhibitors of 5-lipoxygenase-activating protein (FLAP) for the treatment and prevention of atherosclerosis and related disease events

## BACKGROUND OF THE INVENTION

10                   Inhibition of leukotriene biosynthesis has been an active area of pharmaceutical research for many years. Leukotrienes are potent contractile and inflammatory mediators derived by enzymatic oxygenation of arachidonic acid by 5-lipoxygenase.

15                   One class of leukotriene biosynthesis inhibitors are those known to act through inhibition of 5-lipoxygenase (5-LO). In general, 5-LO inhibitors have been sought for the treatment of allergic rhinitis, asthma and inflammatory conditions including arthritis. One example of a 5-LO inhibitor is the marketed drug zileuton (ZYLOFT®) which is indicated for the treatment of asthma. More recently, it has been reported that 5-LO may be an important contributor to the atherogenic process; see Mehrabian, M. et al., Circulation Research, 2002 Jul 26, 91(2):120-126.

20                   A new class of leukotriene biosynthesis inhibitors (now known as FLAP inhibitors) distinct from 5-LO inhibitors was described for the first time in Miller, D.K. et al., Nature, vol. 343, No. 6255, pp. 278-281, 18 Jan 1990, incorporated by reference herein in its entirety. This class inhibits the formation of cellular leukotrienes but has no direct effect on soluble 5-LO activity. These potent agents were used to identify and isolate the inner nuclear membrane 18,000 dalton protein 5-lipoxygenase-activating protein (FLAP). In cells, arachidonic acid is released from membrane phospholipids by the action of cytosolic phospholipase 2. This arachidonic acid is transferred to nuclear membrane bound 5-lipoxygenase by FLAP. The presence of FLAP in cells is essential for the synthesis of leukotrienes.

25                   Despite significant therapeutic advances in the treatment and prevention of atherosclerosis and ensuing atherosclerotic disease events, such as the improvements that have been achieved with HMG-CoA reductase inhibitors such as simvastatin (ZOCOR®), further treatment options are clearly needed. The instant invention addresses that need by providing methods for using FLAP inhibitors for treatment and prevention of atherosclerosis.

## SUMMARY OF THE INVENTION

30                   This invention involves the use of compounds which are FLAP inhibitors, particularly compound I described below, to slow or halt atherogenesis. Therefore, one object of the instant

invention is to provide a method for treating atherosclerosis, which includes halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising administering a therapeutically effective amount of a FLAP inhibitor to a patient in need of such treatment. Another object is to provide methods for preventing or reducing the risk of developing atherosclerosis, comprising administering a prophylactically effective amount of a FLAP inhibitor to a patient who is at risk of developing atherosclerosis. A further object is to provide the use of FLAP inhibitors in combination with other anti-atherosclerotic drugs. Additional objects will be evident from the following detailed description.

## 10 DETAILED DESCRIPTION OF THE INVENTION

Atherosclerosis is characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries. Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

A FLAP inhibitor may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a FLAP inhibitor to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

The method of this invention particularly serves to prevent or slow new atherosclerotic lesion or plaque formation, and to prevent or slow progression of existing lesions or plaques, as well as to cause regression of existing lesions or plaques.

Accordingly, one aspect of this invention involves a method for halting or slowing the progression of atherosclerosis, including halting or slowing atherosclerotic plaque progression, comprising administering a therapeutically effective amount of a FLAP inhibitor to a patient in need of such treatment.

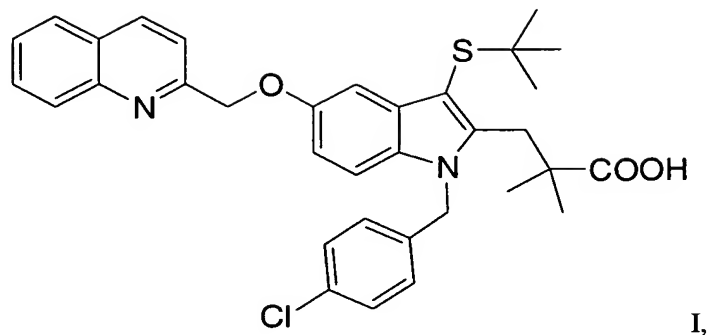
This method also includes halting or slowing progression of atherosclerotic plaques existing at the time the instant treatment is begun (i.e., "existing atherosclerotic plaques"), as well as halting or slowing formation of new atherosclerotic plaques in patients with atherosclerosis.

Another aspect of this invention involves a method for regression of atherosclerosis, including regression of atherosclerotic plaques existing at the time the instant treatment is begun, comprising administering a therapeutically effective amount of a FLAP inhibitor to a patient in need of such treatment.

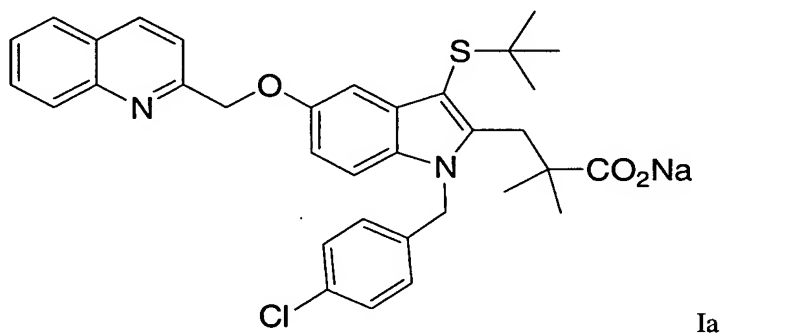
Another aspect of this invention involves a method for preventing or reducing the risk of atherosclerotic plaque rupture comprising administering a prophylactically effective amount of a FLAP inhibitor to a patient in need of such treatment. A further aspect of this invention involves a method for preventing or reducing the risk of developing atherosclerosis, comprising administering a prophylactically effective amount of a FLAP inhibitor to a patient in need of such treatment.

The compounds included within the scope of this invention are FLAP inhibitors including, but not limited to, the compounds disclosed in U.S. Patent No. 5,204,344. In general, FLAP inhibitors can be identified as those compounds which have an IC<sub>50</sub> in the "FLAP Binding Assay" that is less than or equal to 1  $\mu$ M, and preferably 500 nM or less. The FLAP Binding Assay is described in Example 1 below.

Examples of FLAP inhibitors within the scope of this invention are the compounds described in U.S. Patent No. 5,204,344, herein incorporated by reference in its entirety. One example is the compound 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid, shown as compound I:



and the pharmaceutically acceptable salts and esters thereof, and particularly the sodium salt thereof which is known as MK-591 and has the following structure Ia:



5           The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. In addition to the sodium salt Ia depicted above, examples of salts of compound I derived from inorganic bases include but are not limited to aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, zinc and the like. The ammonium, calcium, magnesium, potassium and sodium salts are preferred, and the sodium salt is particularly preferred. Salts derived from

10 pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-sup.1 -dibenzylethylenediamine, diethylamine, 2- diethylaminoethanol, 2- dimethylaminoethanol, ethanolamine, ethylenediamine, N-

15 ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

The term "pharmaceutically acceptable salts" also refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include

acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids are preferred.

5               Ester derivatives of the described compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used herein, references to compound I are meant to also include the pharmaceutically acceptable salts and esters thereof.

10               Additionally, compounds useful in the practice of this invention may exist in amorphous or crystalline forms, and some of the crystalline forms may exist as polymorphs, and as such are intended to be included in the present invention. Furthermore, compounds useful in the practice of this invention may be anhydrous or may form solvates with water or common organic solvents. The use of such anhydrate, hydrate and solvate forms of FLAP inhibitors, including for  
15               example compound I, are likewise encompassed within the scope of this invention.

In addition to several publications which describe MK-591 (such as Brideau C, et al., Can J Physiol Pharmacol. 1992 Jun, 70(6):799-807; and Prasit P. et al, Lipid Mediat, 1993 Mar-Apr;6(1-3):239-44), compounds I and Ia and related compounds, synthetic methods and exemplary pharmaceutical compositions are disclosed in U.S. Patent No. 5,204,344.

20               The term "patient" includes mammals, especially humans, who use the instant active agents for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk of onset of atherosclerosis.

25               The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented  
30               in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

An effective amount of a FLAP inhibitor in the method of this invention is in the range of about 0.001 mg/kg to about 100 mg/kg of body weight per day, preferably 0.01 mg to about 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. A single daily dose is preferred but not necessary. On the other hand, it may be necessary to use dosages outside these limits in some cases.

As examples, the daily dosage amount may be selected from, but not limited to 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg and 250 mg. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the patient's condition. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition. It is expected that the FLAP inhibitor will administered chronically on a daily basis for a length of time appropriate to treat or prevent the medical condition relevant to the patient, including a course of therapy lasting months, years or the life of the patient.

In the method of treatment of this invention, the FLAP inhibitors may be administered via any suitable route of administration such as orally, parenterally, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Oral formulations are preferred.

For oral use, the pharmaceutical compositions of this invention containing the active ingredient may be in forms such as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc.

Oral immediate-release and time-controlled release dosage forms may be employed, as well as enterically coated oral dosage forms. Tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. One example of a time-controlled release device is described in U.S. Patent No. 5,366,738. They may also be coated by the technique described in U.S. Patent No.'s 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said

partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

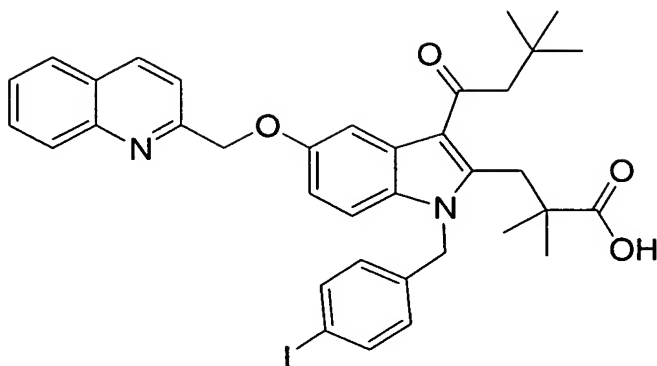
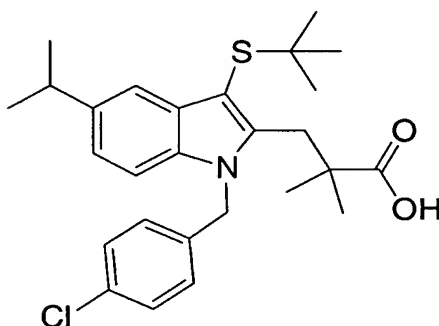
Compounds useful in the method of treatment of the invention may also be administered in the form of a suppository for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

One or more additional active agents, for example but not limited to anti-atherosclerotic agents, may be used in combination with the FLAP inhibitors of this invention in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. The additional active agent or agents can be lipid altering compounds such as HMG-CoA reductase inhibitors, or agents having other pharmaceutical activities, or agents that have both lipid-altering effects and other pharmaceutical activities. Examples of HMG-CoA reductase inhibitors useful for this purpose include statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784); dihydroxy open acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the sodium salt thereof (see US Patent No. 4,346,227); fluvastatin particularly the sodium salt thereof (see US Patent No. 5,354,772); atorvastatin, particularly the calcium salt thereof (see US Patent No. 5,273,995); nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200); and rosuvastatin (also known as ZD-4522, see US Patent No. 5,260,440). Additional active agents which



may be employed in combination with a FLAP inhibitor include but are not limited to 5-lipoxygenase inhibitors, HMG-CoA synthase inhibitors; cholesterol absorption inhibitors such as ezetimibe which is 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, described in U.S. Patent No.'s Re. 37721 and 5,846,966; cholesterol ester transfer protein (CETP) inhibitors, for example JTT-705 and CP529,414; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT1 and -2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) agonists including the compounds commonly referred to as glitazones for example troglitazone, pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR $\gamma$  agonists outside the thiazolidinedione structural class; PPAR $\alpha$  agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual  $\alpha/\gamma$  agonists such as 5-[(2,4-dioxo-5-thiazolidinyl)methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]-benzamide, known as KRP-297; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B<sub>12</sub> (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril; calcium channel blockers such as nifedipine and diltiazam; endothelial antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands including both inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib.

Compounds L-691,831 and MK886 are used in the following assay and have the following structural formulas:

**L-691,831****MK886**

Synthesis of L-691,831 is described in U.S. Patent No. 5,380,850, herein incorporated by reference.  
 Synthesis of MK-886 is described in U.S. Patent No. 5,081,138, herein incorporated by reference.

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### EXAMPLE

#### FLAP Binding Assay

The 100,000 x g pellet from human leukocyte 10,000 x g supernatants (1) was the source of FLAP. The 100,000 x g pellet membranes were resuspended in  
 10 Tris-Tween assay buffer (100 mM Tris HCl pH 7.4, 140 mM NaCl, 2 mM EDTA, 0.5 mM dithiothreitol, 5% glycerol, 0.05% Tween 20) to yield a final protein concentration of 50 µg to 150 µg/ml. Aliquots (100 µl) of membrane suspension were added to 12 mm x 75 mm polypropylene tubes containing 100 µl Tris-Tween assay buffer, 30,000 cpm [<sup>125</sup>I]-L691,831 in 5 µl MeOH:assay buffer (1:1),  
 15 and 2 µl dimethyl sulfoxide or competitor (i.e., the compound to be tested) in dimethyl sulfoxide. MK886 (10 µM final concentration) was used to determine non-specific binding. After a 20 minute incubation at room temperature, tube contents were diluted to 4 ml with cold 0.1 M Tris HCl pH 7.4, 0.05% Tween 20 wash buffer and the membranes were collected by filtration of GFB filters presoaked in

the wash buffer. Tubes and filters were rinsed with 2 x 4 ml aliquots of cold wash buffer. Filters were transferred to 12 mm x 3.5 mm polystyrene tubes for determination of radioactivity by gamma-scintillation counting.

5 Specific binding is defined as total binding minus non-specific binding.

Total binding was [ $^{125}$ I]-L691,831 bound to membranes in the absence of competitor; non-specific binding was [ $^{125}$ I]-L691,831 bound in the presence of 10 uM MK886. Preparation of [ $^{125}$ I]-L691,831 is described in reference 1, below.

The IC<sub>50</sub> values were obtained by computer analysis (see reference 2, below) of the experimental data.

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#### REFERENCES:

1. Charleson, S., Prasti, P., Leger, S., Gillard, J.W., Vickers, P.J., Mancini, J.A., Charleson, P., Guay, J., Ford-Hutchinson, A.W., and Evans, J.F. (1992) Characterization of a 5-lipoxygenase-activating protein binding assay: correlation of affinity for 5-lipoxygenase-activating protein with leukotriene synthesis inhibition. Mol Pharmacol 41:873-879 (herein incorporated by reference).
- 15 2. Kinetic, EBDA, Ligand, Lowry: A collection of Radioligand Binding Analysis Programs by G.A. McPherson. Elsevier-BIOSOFT (herein incorporated by reference).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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